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COMORBIDITY IN RISK AND OUTCOME OF HEMATOLOGICAL MALIGNANCIES

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Comorbidity in risk and outcome of hematological malignancies

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To memory of my father

To my mother

To Elham, Saba and Sina

ABSTRACT

Hematological malignancies are a group of neoplasms that originate from the bone marrow or lymphatic tissues representing close to 10% of the overall cancer burden in the world.

Clinical course, prognosis and survival varies greatly from very aggressive disease requiring intensive systemic chemotherapy-based treatment to indolent forms without need of therapy at diagnosis. Patients are typically diagnosed at old age and may have other comorbid diseases that have to be taken into account for optimal treatment and care. Comorbid diseases may constitute risk factors for the development of subtypes of hematological malignancies, and/or determinants of complications and death. The aim of this thesis was to evaluate the association and impact of comorbid diseases on mortality in leukemia, myeloma and lymphoma, risk of suicidal behavior and death following diagnoses of hematological malignancies, especially considering mental comorbidity, and finally evaluating appendectomy as a potential risk factor for hematological malignancy of lymphoid origin. The study cohorts of the four papers in this thesis were created by linkage between Swedish national health care registers (studies I-III) and the national Swedish quality register for lymphoma (study IV).

In study I, we evaluated risk of attempted and completed suicide in a cohort of 46,309 patients diagnosed with lymphoma, myeloma or leukemia in Sweden 1992-2009 compared with a set of cancer-free individuals using Poisson regression. The relative risk of completed suicide was 3.5-fold increased among patients with myeloma and 1.9-fold increased among patients with lymphoma but not significantly increased among patients with leukemia. Risk of attempted suicide was also increased among patients with myeloma and lymphoma. History of mental disorders conferred highly increased risks.

Next (study II), we evaluated the association and impact of comorbidity in general and specific comorbid diseases (defined according to the Charlson index) on all-cause and cancer-specific mortality in patients with acute myeloid leukemia (AML), chronic myeloid leukemia (CML) or myeloma, accounting for competing risks in analyses of cancer-specific death. Comorbidity was associated with increased all-cause as well as cancer-specific mortality. Disorders associated with higher cancer-specific mortality were renal disease (in AML, CML, myeloma), cerebrovascular conditions, dementia, psychiatric disease (AML, myeloma), liver and rheumatic disease (AML), cardiovascular and pulmonary disease (myeloma).

In study III, we evaluated the association between comorbid disease history and lymphoma characteristics, treatment selection and lymphoma-specific mortality among patients with diffuse large B-cell lymphoma (DLBCL), an aggressive lymphoma subtype. Comorbid patients had a significantly higher relative probability of presenting with low performance status compared with patients without comorbidity, and a lower relative probability of receiving curative treatment, leading to increased risks of all-cause as well as lymphoma-specific death. Among patients selected for curative treatment, comorbid disease was associated with all-cause but not lymphoma-specific death.

Finally, in study IV, in light of mixed results in previous studies, we examined risk of

lymphoid neoplasms in a cohort of 337,437 appendectomized patients <60 years of age in Sweden 1975-2009. We did not observe any clear associations between appendectomy and risk of non-Hodgkin lymphoma overall or major subtypes, myeloma or acute lymphoblastic leukemia. An increased risk of Hodgkin lymphoma was noted among patients diagnosed with appendicitis and for the nodular sclerosis subtype of HL, which could reflect a true association, or shared susceptibility to infection/inflammation among individuals prone to develop HL.

LIST OF SCIENTIFIC PAPERS

This thesis is based on following manuscripts which will be referred to in the text by their roman numerals (I-IV):

- I. **Mohammadi M**, Moradi T, Bottai M, Reutfors J, Cao Y, Smedby KE.
Risk and predictors of attempted and completed suicide in patients with hematological malignancies.
Psychooncology. 2014 Nov;23(11):1276-82
- II. **Mohammadi M**, Cao Y, Glimelius I, Bottai M, Eloranta S, Smedby KE.
The impact of comorbid disease history on all-cause and cancer-specific mortality in myeloid leukemia and myeloma - a Swedish population-based study.
BMC Cancer. 2015 Nov 5;15:850
- III. **Mohammadi M**, Eloranta S, Glimelius I, Cao Y, Jerkeman Mats, Bottai M, Smedby KE.
Comorbid disease history and associations with disease characteristics, treatment intent and mortality in diffuse large B-cell lymphoma – a Swedish lymphoma register study.
Manuscript
- IV. **Mohammadi M**, Song H, Cao Y, Glimelius I, Ekbom A, Ye W, Smedby KE.
Risk of lymphoid neoplasms in a Swedish population-based cohort of 337,437 patients undergoing appendectomy.
Scand J Gastroenterol. 2015 December;51(5):583-9 (E-pub)

CONTENTS

1	Introduction	1
2	Background.....	3
2.1	Leukemia	3
2.1.1	Acute lymphoblastic leukemia (ALL).....	3
2.1.2	Acute myeloid leukemia (AML)	4
2.1.3	Chronic myeloid leukemia (CML)	4
2.2	Lymphoma.....	5
2.2.1	Hodgkin lymphoma (HL)	5
2.2.2	Non-Hodgkin lymphoma (NHL).....	5
2.3	Myeloma.....	7
2.4	Suicide	7
2.5	Comorbidity.....	7
2.6	Appendectomy.....	9
3	Aims of the thesis	11
3.1	General aim.....	11
3.2	Specific aims.....	11
4	Patients and methods	12
4.1	Patients.....	12
4.1.1	The Swedish national registers	12
4.1.2	Quality register	13
4.2	Study design	13
4.2.1	Study I.....	13
4.2.2	Study II	14
4.2.3	Study III.....	14
4.2.4	Study IV.....	15
4.3	Ethical considerations.....	19
5	Results.....	21
5.1	Study I.....	21
5.2	Study II	22
5.3	Study III:	25
5.4	Study IV	28
6	Discussion.....	31
6.1	Interpretation of findings.....	31
6.1.1	Study I.....	31
6.1.2	Study II	31
6.1.3	Study III.....	33
6.1.4	Study IV.....	33
6.2	Methodological considerations	34
6.2.1	Study I.....	34
6.2.2	Study II	34
6.2.3	Study III.....	35

6.2.4	Study IV	35
7	Conclusions and future perspectives	36
7.1	Conclusions	36
7.2	Future perspectives.....	36
8	Acknowledgements	37
9	References	39

LIST OF ABBREVIATIONS

ACE27	Adult comorbidity evaluation 27 index
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CCI	Charlson comorbidity index
CHOP	Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone
CHOP-R	Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone, Rituximab
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CPD	Chronic Pulmonary disease
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
HCT-CI	Hematopoietic-cell transplantation specific comorbidity index
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
ICD	International Classification of Diseases
IPI	International prognostic index
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasms
MRR	Mortality rate ratio
NHL	Non-Hodgkin lymphoma
RRR	Relative risk ratio
S-LD	Serum lactate dehydrogenase
SEK	Swedish Kronor
SIR	standardized incidence ratio
SLL	Small lymphocytic leukemia
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organization

1 INTRODUCTION

Hematological malignancies represent a heterogeneous group of neoplasms with regard to etiology and molecular biology as well as treatment, clinical course and survival and therefore constitute a large challenge for patients, their families, and the physicians (oncologists/hematologists) caring for them. Together, they represent close to 10% of incident cancers worldwide [1]. From a public health viewpoint, in Sweden in 2002, total costs of, e.g. acute myeloid leukemia (AML), one of the most aggressive forms of hematological malignancies, was estimated to generate direct costs of 225 million SEK and indirect costs of 236 million SEK [2].

Several known/suggested risk factors for hematological malignancies have been presented but most cases remain unexplained. A range of disorders affecting the lymphatic system and immune response, including most notably HIV/AIDS, organ transplantations, but also less severe states of immune perturbation such as autoimmune and chronic inflammatory conditions and infections, constitute risk factors for several subtypes of hematological malignancies. Other risk factors include smoking and ionizing radiation. The appendix is rich in lymphatic tissue and appendectomy and its common cause, appendicitis, has been suggested as a possible risk for hematological malignancies of lymphoid origin in some studies [3-7].

Whereas some specific comorbid disorders are clearly of etiologic relevance in hematologic malignancies and may alter biology and clinical course, many other common comorbidities still constitute important factors that can affect treatment selection, prognosis and survival [8-16]. The incidence of most subtypes of hematological malignancies increases with age, as is the case with many chronic diseases as well as other cancer forms. However, as opposed to solid cancer where successful primary treatment is often based on radical surgical excision, treatment in hematological malignancies typically rely on prolonged chemotherapy-based treatment schedules with toxic effects on vital organs including the kidney, liver, heart and lungs. Worse outcomes among cancer patients with comorbidities, and perhaps especially among patients with hematological malignancies, can therefore be expected, nevertheless needs to be managed as optimally as possible. Cancer patients are also known to be at increased risk of suicide. Suicide is an avoidable cause of death that is believed to complicate cancer because of high level of distress after a cancer diagnosis in itself, but may also be related to uncontrolled pain and other physical symptoms and the prognosis of the cancer diagnosed [17-25]. Few previous studies have addressed potential variation in risk of suicide among patients with different subtypes of hematological malignancies.

In this thesis, we evaluated risk of suicide in patients with hematological malignancy subtypes, associations and impact of comorbid disease histories with mortality in leukemia and myeloma, associations with lymphoma characteristics, treatment intent and mortality in diffuse large B-cell lymphoma, and lastly the potential association between appendectomy and risk of hematological malignancies of lymphoid origin.

2 BACKGROUND

Hematological malignancies originate from myeloid or lymphoid cells residing in the bone marrow or lymphatic tissues. Major malignancy types in this group primarily include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and malignant lymphomas. According to the most recent and widely adopted WHO classification system the group of lymphomas includes a number of sub entities, for example chronic lymphocytic leukemia (CLL) and multiple myeloma, although according to the International Classification of diseases (ICD), these last entities are coded as separate disorders.

Studies to date suggest that environmental factors may play a larger role in the etiology of leukemia and lymphoma than genetic factors, although family history and low penetrance genetic traits are of importance as well [26-33]. However, for most newly diagnosed cases, the etiology is elusive, and therefore, efforts to identify potential etiologies remain an active research area.

Cure is often a realistic goal of treatment for leukemia and lymphoma, especially in younger patients. Survival has increased in recent years across all age categories partly through the use of new treatment protocols, including immunological and more recently also biological therapies [34].

2.1 LEUKEMIA

Leukemia is a malignant transformation of white blood cells to leukemic cells. Leukemic cells replace normal bone marrow cells and consequently decrease/suppress hematopoiesis and patients therefore often present with anemia, thrombocytopenia and granulocytopenia. Organomegaly such as hepatomegaly, splenomegaly and lymphadenopathy are also common. Leukemias are divided into acute forms characterized by immature poorly differentiated cells, and chronic forms characterized by more mature cells. Myelodysplastic syndromes are disorders of bone marrow transformation where the blast count is less than a definite diagnosis of AML.

The incidence of leukemia overall varies between racial and ethnic groups with different genetic make-ups. Incidence rates are highest in the United States, Australia, and Germany and intermediate in most European countries [35]. In Europe 2012, the highest incidence was reported in Cyprus (15.9/100,000 for men and 9.7/100,000 for women) and the lowest in Bosnia Herzegovina (4.3/100.000 for men and 3.3/100,000 for women) [36].

Chemical agents such as benzene and formaldehyde, air pollution [37-41], smoking [42-44] and obesity [45] have been demonstrated to increase risk of leukemia.

2.1.1 Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia is the most common malignancy in childhood, and about half of the cases occur in childhood and teenagers, and half in adults. The age-adjusted overall

incidence rate of ALL in the United States is 1.5 per 100 000 [46, 47]. In 2014, incidence rates were 1.4 for males and 1.2 for females per 100,000 in Sweden [48]. Individuals with Down's syndrome are at increased risk [49].

5-year survival (2005-2011) reported from the USA was 70.1% [50]. Treatment of ALL includes several chemotherapy phases. The first step is remission induction aiming to eliminate the bulk- leukemia cell population. Remission induction may be repeated if the patient is not in remission. The next phase is consolidation therapy [51], and the last step is maintenance therapy.

2.1.2 Acute myeloid leukemia (AML)

The incidence of AML increases with age [2], and the median age at diagnosis is around 69 years [52]. It is more common among males than among females [52]. In 2014, the incidence rate was 3.1 for males and 2.6 for females per 100,000 in Sweden [48]. Environmental risk factors include ionizing radiation, magnetic fields and cigarette smoking [53-61]. Risks are also increased following post organ transplant immune suppression [62]. The molecular heterogeneity of AML is increasingly recognized. The current WHO classification recognizes four major categories (AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML and AML not otherwise specified), but a revision is under way.

Treatment primarily includes intensive induction chemotherapy, and post-remission consolidative therapy with conventional chemotherapy or hematopoietic-cell transplantation [63]. Outcome depends on the pathobiology of AML and genetic abnormalities, age, performance status and comorbid diseases. Patients older than 60-70 years may not be eligible for intensive treatment. By age group, 24% of 75-84 year-olds and 6% of patients older than 85 years received intensive treatment in Sweden, and otherwise, the patients received a less toxic dose of chemotherapy [64, 65]. 5-year survival (2005-2011) reported from USA was 26.0%.

2.1.3 Chronic myeloid leukemia (CML)

Median age at diagnosis of CML is approximately 60 years. CML is uncommon, and in 2014, incidence rates were 1.3 for males and 0.9 for females per 100,000 in Sweden [48]. Risk factors for CML include ionizing radiation [66], and organ transplantation [62].

Survival of patients with CML has improved dramatically after the introduction of tyrosine kinase inhibitors in the beginning of the 21st century. Imatinib as the first member of tyrosine kinase family replaced cytoreductive therapies and interferon used as traditional treatments for CML [67, 68]. In Sweden, 5-year survival in the period of 2002-2010 was 81% and for patients diagnosed in a chronic phase the 5-year survival was 83% [69].

2.2 LYMPHOMA

Lymphoma is a malignancy of the lymphatic system. Malignant lymphomas constitute the most common hematological malignancies in adults. Traditionally, there are two main categories of lymphomas, the non-Hodgkin lymphomas (NHL, 90%), and Hodgkin lymphoma (HL, 10%). NHL represent clonal expansions of B-, T- or NK cells, of which B-cell NHLs are by far the most common. The hallmark of HL tumors is the presence of the Reed-Sternberg cells, recently shown to be of B-cell origin.

The Ann Arbor staging system is used to classify disease spread and provides a basis for prognostic evaluation and treatment selection for both HL and NHL patients [70, 71]. According to Ann Arbor, lymphomas are classified into 4 stages based on localization of malignancy. Primary extranodal NHL are classified according to the Musshoff system.

Table 1. Ann Arbor staging system

Ann Arbor Staging system	
Stage	
I	Involvement of a single lymph node region
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Diffuse or disseminated extra nodal involvement

2.2.1 Hodgkin lymphoma (HL)

The highest incidence rates are found in Yemen and Lebanon at >5.5 per 100,000. The incidence rate in Sweden is 2.1 per 100,000 for males and 1.7 per 100,000 for females [72]. Previous studies showed that patients with HIV/AIDS [73], delayed infection with Epstein-Barr virus (mononucleosis) [74] and smokers [75, 76] are at increased risk of HL. Genetic variation in the human leukocyte antigen (HLA) region is also associated with HL risk [77]. HL is highly sensitive to chemotherapy and radiotherapy. The main cause of death in patients is the adverse effect of treatment such as cardiovascular and secondary cancer [78-80]. 5-year survival (2005-2011) reported from USA was 88.3%.

2.2.2 Non-Hodgkin lymphoma (NHL)

NHL are a group of heterogeneous malignancies arising from lymphocytes residing in lymph nodes, bone marrow or in any organ of the body. Diffuse large B-cell lymphoma and follicular lymphoma are the most common subtypes of NHL, but they can be further subdivided into more than 40 groups according to WHO classification (2008). Clinically, NHL is subdivided into indolent and aggressive forms. The indolent types progress slowly and are seldom possibly to cure. The aggressive types progress fast but response well to

treatment in most instances. Follicular lymphomas represent a common indolent group whereas diffuse large B-cell lymphomas (DLBCL) are aggressive.

The highest incidence rates of NHL are observed in Northern America (16.9 per 100,000), Australia and New Zealand (14.3 per 100,000) and Western Europe (11 per 100,000). The incidence rate in Sweden is 14.7 per 100,000 for males and 10.3 per 100,000 for females [72]. Risk factors include family history, strong immune suppression (HIV/AIDS, organ transplantation, rare inherited immunodeficiency syndromes) but also disorders of immune activation [81]. Treatment of NHL is based on combination chemotherapy, immunotherapy (most notably anti-CD20 antibodies) and radiotherapy. 5-year survival (2005-2011) reported from USA was 71.9%.

2.2.2.1 Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common subtype of NHL [82]. The 5-year survival in Sweden has been reported to range from 74 percent among patients younger than 40 years to 22 percent among patients older than 79 years [82]. The disease is aggressive and requires rapid initiation of intensive treatment. The standard treatment for DLBCL is 14 or 21 day cycle of rituximab with, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP-14 or R-CHOP-21) [83]. For prophylaxis against central nervous system recurrence, intrathecal methotrexate and cytarabine and intravenous methotrexate has been recommended [83]. Positron emission tomography (PET) scan is used with increasing frequency for evaluation of treatment response.

The International Prognostic Index (IPI) has been developed to predict prognosis and guide treatment decisions in DLBCL [84]. Accordingly, age older than 60, Ann Arbor Stage III or IV, elevated serum-lactate dehydrogenase (LD), performance status 2, 3 or 4 and having more than one extra nodal disease location are considered as risk factors [84]. Recently, a refined IPI (NCCN-IPI) was suggested based on patients treated during the rituximab-era, proposing further refinement by age and by certain major extranodal locations including the central nervous system (CNS), bone marrow, lung and the gastrointestinal tract including liver [85].

2.2.2.2 Follicular lymphoma

Follicular lymphoma is the most common indolent subtype of NHL. Asymptomatic patients are managed with a watch-and-wait policy. For symptomatic patients, Rituximab as monotherapy or in combination with chemotherapy is the first line treatment in Sweden [86]. In Sweden, 5-year and 10-year survival for patients aged <60 years in the period 2003-2010 were 91% and 83%, respectively [86].

2.2.2.3 Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL, hereafter only denoted CLL)

CLL is a disease involving lymphocytes in the bone marrow, lymph nodes and other organs, and is mostly of B-cell type. Lymphocytosis in the blood distinguishes CLL from SLL. CLL

affects males twice as frequently as females [87]. In 2008, the incidence rate was 6.5 for male and 3.1 for female per 100000 in Sweden [48]. Family history is a clear risk factor for CLL [33, 88, 89]. CLL does not need to be treated if asymptomatic. If blood counts decrease and symptoms occur, treatment includes chemotherapy, immunotherapy and/or radiotherapy. The 5-year survival (2005-2011) in the USA was 84.8%.

2.3 MYELOMA

Multiple myeloma and the localized form plasmacytoma, is a malignancy of the plasma cell, an antigen-producing B cell. Transformed plasma cells accumulate in the bone marrow and cause several clinical characteristics of myeloma such as anemia and bone pain. Accumulation of paraproteins may lead to amyloidosis and/or renal failure. Asymptomatic myeloma is routinely not treated. Patients with symptomatic myeloma require chemotherapy and/or immunomodulatory therapy. Intensive treatment with hematopoietic-cell transplantation are options for younger patients.

Multiple myeloma is the second most prevalent hematological malignancy after NHL. It is more common in men than women. In the USA the incidence is 7.1 per 100 000 in men and 4.6 per 100 000 in women. [90]. In Sweden, age standardized incidence rate is 7.7 per 100,000 for men and 5.1 per 100,000 for women [48]. In previous studies, hair coloring [91], pesticides [92], obesity [92], pernicious anemia and ankylosing spondylitis [92, 93] and family history [94] have been suggested as risk factors for myeloma. 5-year survival (2005-2011) reported from USA was 48.5%.

2.4 SUICIDE

Suicide is the third cause of death among young adults (ages 15-44 years) leading to one million avoidable deaths worldwide every year [95]. Completed suicide may be preceded by one or several suicide attempts. The rate of attempted suicide is higher than completed suicide [96]. Age, gender and ethnicity influence suicide rates [97-99], and a range of additional predictors of suicidal behavior have also been described in the literature including psychiatric disorders and substance abuse, severe somatic disorder, uncontrolled pain, chronic or bad prognosis disease such as cancer, lack of social support, unemployment, and socioeconomic factors such as migration [100-106]. Higher suicide rates shortly after diagnosis of cancer including hematological malignancies have been reported in several studies [1, 17-23, 107, 108]. However, few previous studies considered risks by subtypes of hematological malignancies. Given the large differences in levels of treatment and care among patients with hematological malignancies, subtype-specific risks are needed to inform health care personnel caring for these patients.

2.5 COMORBIDITY

Disorders involving the heart, lungs, liver or kidneys represent an additional challenge to the treating physicians since cancer patients with such comorbidities can be expected to have a lower tolerance to standard chemotherapy-based regimens. Therefore, a common clinical

problem at diagnosis of adult and elderly patients is to evaluate comorbid disease history in relation to treatment channeling, prognosis and survival.

Severe comorbid disease increases overall mortality in cancer patients [109-113] including patients with hematological malignancies [8-12, 114]. However, among patients with hematological malignancies, there is a focus on studies of patients eligible for hematopoietic stem cell transplantation [14-16, 115], excluding many elderly patients. Fewer studies have addressed if comorbidities also increase risks of cancer-specific mortality. A Danish study reported that severe comorbidity increases overall but not cancer-specific mortality among colorectal and prostate cancer patients but increases both overall and cancer-specific mortality in lung cancer cases [109, 110]. Among patients with AML, history of comorbid disease is associated with overall survival and with complete remission rates [10-12]. In some but not all studies, a worse survival was noted among NHL and DLBCL patients with a high comorbidity index as measured with different scales [118-120]. A recent study found that rheumatoid arthritis improved prognosis in NHL [116]. In contrast another cohort study from Sweden reported decreased survival times in NHL [117].

Comorbid diseases may affect overall and cancer-specific survival through biological mechanisms if they are related to disease etiology, as is the case, e.g. in HIV/AIDS and organ transplantation leading to increased risks specifically of EBV-driven aggressive NHL [81]. However, and more importantly in terms of patient numbers, comorbidity in general may affect treatment tolerability and choice of treatment intensity as well as modality. In investigations of associations and impact of comorbidity in general on cancer outcomes, choices have to be made about the scope and measurement of comorbid diseases. To this end, researchers have presented several models to define and measure comorbid diseases.

Charlson Comorbidity Index (CCI): In 1987, Charlson et al. developed a model for estimating effects of comorbid disease on mortality in non-cancer patients, revised later by other researchers for use based on administrative data [118, 119]. Charlson classified the comorbid diseases in 19 groups and assigned a score from 1 to 6 to each disease in order to capture the number and severity of the diseases [118]. This index has become widely used.

Elixhauser comorbidity model: In 1998, Elixhauser presented a comorbidity adjustment model including 30 comorbid diseases. Elixhauser expanded the comorbidity list with, e.g., mental disorders, drug and alcohol abuse, coagulopathies, and fluid and electrolyte disorders [120].

The Adult Comorbidity Evaluation 27 index (ACE27): The ACE27 includes 27 comorbid diseases and a grading of severity into 3 grades: mild, moderate and severe [121].

Hematopoietic cell transplantation (HCT)-specific comorbidity index (HCT-CI): This is a modified version of CCI for predicting the prognosis in candidates for hematopoietic-cell transplantation [122].

2.6 APPENDECTOMY

Appendix is a part of the secondary lymphoid tissues and a place for presenting food-, drug- and microorganism-antigens to the blood and lymphoid system [123]. Appendectomy is still one of the most common surgical procedures around the world [124] and potential long term consequences of this procedure are therefore important to investigate. Given its role in the immune system, removal of the appendix may have immunological consequences, and some studies reported immunoglobulin changes after appendectomy [125, 126].

In 1964, MacWay observed an increased risk of cancer after appendectomy in an autopsy study [127]. He then hypothesized a protective role of appendix against carcinogen viruses [3]. However, some negative studies followed [128, 129]. With regard to hematological malignancies, Hyams reported a higher prevalence of HL, and later, Cope et al. reported an increased risk of NHL among patients younger than 20 years, following appendectomy [4, 6]. However, yet other studies have reported no increase in risks of hematological malignancies after appendectomy [5, 130-132]. Appendectomy and/or appendicitis could potentially be associated with risk of hematological malignancies through immune dysfunction [133-135], inflammation and infection [6, 136, 137] and/or other effects related to the gut microbiome [138, 139].

3 AIMS OF THE THESIS

3.1 GENERAL AIM

The overall aim of the thesis was to increase knowledge of the association between comorbidities and outcome in hematological malignancies, including suicide, as well as to study the potential role of appendectomy in risk of hematological malignancies of lymphoid origin.

3.2 SPECIFIC AIMS

- To evaluate the risk of attempted and completed suicide following diagnosis of hematological malignancies, and potential effect modification by host factors and comorbidity;
- To study the effect of comorbid diseases on all-cause, cancer-specific and other-cause mortality in leukemia and myeloma;
- To examine the association between specific comorbid diseases with cancer-specific mortality in leukemia, myeloma and diffuse large B-cell lymphoma;
- To study the relationship between comorbidity and lymphoma characteristics, treatment selection and mortality in patients with diffuse large B-cell lymphoma;
- To study the risk of lymphoid neoplasms in patients undergoing appendectomy.

4 PATIENTS AND METHODS

4.1 PATIENTS

4.1.1 The Swedish national registers

Study cohorts were created through linkage between the Swedish Cancer Register, the Swedish Patient Register, the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), the Swedish Cause of Death register and the Swedish Total Population register. For study III, the cohort was defined using the national quality register of lymphoma. The linkages were completed with help from Statistics Sweden and the National Board of Health and Welfare through the unique personal identification numbers assigned to Swedish residents, which have been replaced by serial numbers and a code key.

4.1.1.1 The Swedish Cancer Register

The Swedish cancer register started in 1958 and covers the total population. By law, all health care providers have to report newly diagnosed cancer cases diagnosed in hospitals, clinics or laboratories. The register includes data on sex, age, place of residence, type of cancer, date of diagnosis, stage (from 2004), hospital and department with approximately 96% coverage.

4.1.1.2 The Swedish Patient Register

The Swedish patient register was established regionally in 1964, and covers the whole country from 1987. The register contains information on dates of admission to and discharge from hospitals, main and secondary diagnoses based on ICD codes [140]. Starting in 2001, this register now also records outpatient visits in non-primary health care.

4.1.1.3 LISA

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) is kept by Statistics Sweden and includes data on education level, income and marital status. The register is updated annually and holds data from 1990.

4.1.1.4 The Swedish Cause of Death Register

The Cause of Death Register started in 1961 and contains main cause of death, secondary causes of death, place, age and date of death [140]. All deaths of registered residents are recorded even if they die outside of the country. ICD codes are used to record causes of death based on death certificates.

4.1.1.5 The Swedish Total Population Register

This register was initiated in 1964 and includes data such as sex, citizenship, date of birth, date of death, country of birth, and dates of immigration and emigration [141]. The register covers the entire population of Sweden and is updated on a daily basis.

4.1.2 Quality register

4.1.2.1 *The national quality register for lymphoma*

The national Swedish quality register for lymphoma was established in 2000 and holds data on subtype of lymphoma according to the WHO classification, stage of disease (according to Ann Arbor), date of diagnosis, extranodal sites, bulky disease, serum-lactate dehydrogenase (S-LD), performance status, B symptoms and primary treatment intent (curative/palliative)[142]. Since 2007, the register also holds data on primary treatment modality, chemotherapy regimen and treatment response. A validation of registered lymphoma characteristics at diagnosis was carried out in 2010 through medical record review and showed generally high concordance (80-90%) (personal communication Dr Szekely, Skåne University Hospital Malmö).

4.2 STUDY DESIGN

4.2.1 Study I

Population: All patients with a first diagnosis of a hematological malignancy 1992 to 2009 at 15 years of age or older were included in the main study cohort (patients with diagnosis at autopsy were excluded) (N=46,309). We also included a random sample of patients >15 years of age with solid cancers representing 10% of these patients diagnosed 1992 to 2009 (N=61,552). For each cancer patient, one comparison individual with the same sex and birth year was randomly selected (N=107,736). The comparison individuals further had to be alive and free of cancer at the time of the patients' diagnoses.

Exposure: The main exposure of interest was a diagnosis of a hematological malignancy including ALL, AML, CML, myeloma/plasmacytoma, HL and NHL (including CLL). Secondary exposure was a diagnosis of a solid cancer.

Outcome: Main outcomes were attempted suicide (defined based on hospital admission codes in the patient register) or completed suicide (defined based on cause-of-death register codes) following a diagnosis of cancer, and in comparison individuals following the date of diagnosis of the matched cancer case. (ICD codes can be found in the supplement to study I).

Statistical methods: The association between a diagnosis of a hematological malignancy/solid cancer and attempted or completed suicide was estimated in a Poisson regression model and expressed as incidence rate ratios (IRR) with 95% confidence intervals (CI). The Poisson model is a type of linear model with the assumption that the outcome event follows a Poisson distribution. Age, sex, migration status, total number of years of education, calendar period of diagnosis of cancer, and history of mental disorders were included as the potential confounders in the multivariable model. We also tested for interaction effects by introducing interaction terms in the model.

4.2.2 Study II

Population: All patients aged >18 years, with a first diagnosis of AML, CML or myeloma from 2002 to 2009 in Sweden were included in the cohort except those with a history of hematopoietic-cell or solid organ transplantation, or those diagnosed at autopsy (N=8,135).

Exposure: The Swedish Patient Register was used to collect information on hospitalizations and outpatient visits due to comorbid diseases during a period of 5 years prior to the diagnosis of leukemia/myeloma. The comorbid diseases included cardiovascular disease, diabetes mellitus, cerebrovascular disease, chronic pulmonary disease (CPD), peripheral vascular diseases, peptic ulcer disease, rheumatologic disease, renal disease, liver disease, dementia, hemiplegia/paraplegia and HIV/AIDS in line with diagnoses listed according to the Charlson index and modifications for use in administrative data by Quan et al, with the addition of psychiatric disorders. History of rheumatologic and renal diseases during the year leading up to the diagnosis of leukemia and myeloma were disregarded. The cancer register was used to assess previously diagnosed solid cancers at any time point before the diagnoses of leukemia/myeloma.

Outcome: The Cause-of-Death register was used to obtain date of death and main cause of death. Death due to leukemia/ myeloma was classified as cancer-specific death otherwise deaths were defined as other-cause deaths. We used the principle outlined by Howlader et al. [143] when defining cancer-specific death, classifying also, e.g. leukemia unspecified as cancer-specific death in patients with AML or CML.

Statistical methods: We estimated the association of any comorbid disease history, and number of comorbid diseases with all-cause, cancer-specific and other-cause death following a diagnosis of leukemia/myeloma in a Poisson regression model, and the association was expressed as Mortality Rate Ratios (MRR) with 95% CIs. We also estimated the effect of the specific comorbid diseases on survival using all patients without the specific type of comorbid disease as reference. The probability of cause-specific and other-cause death in the presence of competing risks was estimated for patients aged 60-69, 70-79 and 80-89 years, among men and women separately, using flexible parametric survival models with 95% CI to be able to fit time dependent and non-proportional effects better. Using flexible parametric model, we could calculate the smooth estimates of cause-specific hazards and the cumulative incidence function. When we estimated survival in the presence of competing cases of death, cubic splines were used to model the log baseline cumulative hazard [144].

4.2.3 Study III

Population: All patients aged >18 years with diffuse large B-cell lymphoma (DLBCL) as the first primary hematological malignancy 2004-2009, during the Rituximab era, was defined using the national Swedish quality register for lymphoma (N=3,177). Patients diagnosed with DLBCL at autopsy or with a history of hematopoietic-cell or solid organ transplantation were excluded from the study.

Exposure: Through linkage of the study population to the Swedish Patient Register, we gathered information on hospital admissions and non-primary outpatient visits with codes of comorbid disease (according to modified Charlson index [118, 119] with the addition of psychiatric disorders) during a period of 5 years prior to the diagnosis of DLBCL.

Outcome: The main outcome was lymphoma characteristics at diagnosis (stage, IPI, LD, bulky disease and adverse extranodal location), and treatment intent (curative or palliative). Secondary outcome was death due to lymphoma or other causes. Main underlying death causes and dates of death were collected from the Swedish Cause of Death Register. Patients were followed from the date of diagnosis of DLBCL until emigration, death or December 31st 2012, whichever occurred first.

Statistical methods: Associations with comorbidity and lymphoma characteristics at diagnosis and treatment intent were estimated using multinomial regression, a type of logistic regression that allows for the prediction of outcome variables with more than two categories. In this model, the host, lymphoma and treatment factors were included as outcome factors, and comorbid disease history was treated as an explanatory variable (yes/no), further adjusted for age and sex at diagnosis. From each model, we predicted the probability of the outcome for patients with and without comorbidities, respectively, assuming that age at diagnosis was fixed at the mean level in the cohort. Then, we estimated the relative risk ratios (RRR) (also interpretable as relative probabilities), of the outcome factors. In the multinomial regression, if the outcome is dichotomous, the resulting relative risk in fact represents an odds ratio (OR). As a secondary outcome, we assessed the relative risk of death (all-cause, lymphoma-specific, other-cause) by comorbidity using Mortality Rate Ratios (MRR) with 95% CIs in a Poisson regression model. Analyses were performed among all patients, and separately among patients treated with curative intent.

4.2.4 Study IV

Population: We identified patients who had undergone appendectomy from 1975 to 2009 in Sweden from the Swedish Patient Register (N=337,437). Patients aged 60 years or older at appendectomy, with a history of lymphoid neoplasms before appendectomy, or with less than one year of follow-up were excluded from the study.

Exposure: Patients treated with appendectomy were first subdivided in two major exposure groups: those who had appendectomy alone and those who had appendectomy performed in parallel with other surgical procedures. Next, the medical discharge diagnoses codes were considered (including appendicitis, perforated/abscessed or not, mesenteric lymphadenitis and other diagnoses).

Outcome: using linkage with the Swedish Cancer Register, we identified first incident diagnoses of lymphoid neoplasms including NHL overall (including CLL), HL, myeloma (multiple myeloma, plasmocytoma) or ALL. Patients with lymphoid neoplasms diagnosed

during the first year after appendectomy were excluded. Additionally, using Systematized Nomenclature of Medicine (SNOMED) codes available from 1993 and onwards, major subtypes of NHL (DLBCL, follicular lymphoma, other B-cell NHL as one group and T-cell lymphoma) were classified.

Statistical methods: We calculated the relative risk of lymphoid neoplasms compared with the corresponding stratum-specific incidences in the general population using standardized incidence ratios (SIRs) with 95% CI, under the assumption that cases followed a Poisson distribution. The patients were thus followed from one year after appendectomy until the date of diagnosis of a lymphoid neoplasm, first emigration date, death or December 31st 2009 (end of follow up), whichever occurred first. Separate analyses were performed among individuals aged <20 years of age at appendectomy.

Table 2. Overview of patients and methods included in studies I-IV

	Study I	Study II	Study III	Study IV
Type of study	Register-based cohort study (study I-IV)			
Number of patients	Leukemia: 7,160 Myeloma: 8,444 Lymphoma: 30,705 Other cancers: 61,552	AML: 2,550 Myeloma: 4,584 CML: 1,000	DLBCL: 3177	337,437
Number of comparators	107,736	-	-	General population
Ages	≥ 15	≥ 18	≥ 18	All ages
Study period	1992-2009	2002-2009	2004-2009	1975-2009
Data sources	Cancer Register Patient Register LISA Cause of Death Register	Cancer Register Patient Register LISA Cause of Death Register	Lymphoma Register Cancer Register Patient Register LISA Cause of Death Register	Cancer Register Patient Register
Exposure	Cancer	Comorbid disease	Comorbid disease	Appendectomy
Outcome	Suicidal behaviors	All cause and cancer specific mortality	Treatment type, IPI, Stage, Performance status, all cause and cancer specific mortality	Lymphoid neoplasms
Statistical models	Poisson regression	Poisson regression Flexible parametric model	Poisson regression Multinomial regression	Poisson regression

4.3 ETHICAL CONSIDERATIONS

All four studies were approved by the Regional Board of the Ethical Committee, Stockholm. (Study I: 2005/726-31, 2009/587-32, 2014/1026-32; study II-III: 2007/1335-31/4, 2010/1624-32; study IV: 2014/94-31/2). All studies are register-based studies and, according to present Swedish regulations, individual informed consent is not needed in order to access register data for research purposes. The researchers have not had access to personal identifications numbers, only to pseudonymised data. This coded data has been handled in line with applicable rules and regulations at the Karolinska Institutet in order to preserve data integrity.

5 RESULTS

5.1 STUDY I

For details, please see the appended publication (PMID: 24789427). In summary, in the identified cohort of 46,309 patients with hematological malignancies, we found a statistically significant 45% increased risk of attempted suicide (IRR=1.45, 95% CI=1.18-1.77) and a 2-fold increased risk of completed suicide (IRR=2.06, 95% CI=1.51-2.81) (Table 2) compared with cancer free subjects. In analysis of subgroups of patients with hematological malignancy subtypes, we observed significantly increased risks of attempted suicide among patients with myeloma (IRR=2.13, 95% CI=1.39-3.26) and lymphoma (IRR=1.34, 95% CI=1.07-1.69). For completed suicide, the adjusted risk was increased among patients with lymphoma (IRR=1.87, 95% CI=1.31-2.67), and myeloma (IRR=3.52, 95% CI=2.05-6.03) compared with the cancer-free cohort. For patients with leukemia, point estimates of risk of attempted and completed suicide were increased to a similar level as patients with lymphoma, but the estimates were not statistically significant. Due to small numbers, it was not meaningful to stratify patients further by subtype of leukemia (AML, CML). Risk of attempted and completed suicide among patients with hematological malignancies overall (compared with cancer-free individuals) was increased to a similar extent as in other cancer patients when treated as one group. In the sample of other solid cancer patients, risk of attempted suicide was 48% increased (IRR=1.48, 95% CI=1.24-1.77), and risk of completed suicide was 89% increased (IRR=1.89, 95% CI=1.42-2.51) compared with cancer-free individuals.

Table 3. Relative risk¹ of attempted and completed suicide among patients with hematological malignancies, and in a random sample of patients with other types of cancer, compared with cancer-free individuals.

	Attempted suicide			Completed suicide		
	No. of events	Incidence /10,000 py	IRR (95% CI) ¹	No. of events	Incidence /10,000 py	IRR (95% CI) ¹
Cancer free	360	4.25	1.00	125	1.44	1.00
All hematological malignancies	146	6.86	1.45 (1.18-1.77)	63	2.95	2.06 (1.51-2.81)
Leukemia	17	7.70	1.42 (0.87-2.32)	5	2.26	1.82 (0.72-4.59)
Myeloma	24	8.30	2.13 (1.39-3.26)	15	5.18	3.52 (2.05-6.03)
Lymphoma	105	6.49	1.34 (1.07-1.69)	43	2.65	1.87 (1.31-2.67)
Other cancers	192	6.16	1.48 (1.24-1.77)	88	2.82	1.89 (1.42-2.51)

¹ Incidence Rate ratios (IRR) with 95% confidence intervals (CI), adjusted for sex, age, calendar period, education, migration status and history of mental disorders before diagnosis of cancer.

History of mental disorders or suicide attempts was associated with approximately 15 to 30-fold increased risks of attempted as well as completed suicide compared with cancer-free individuals without such history (Table 3), although formal tests for interaction were not statistically significant. Importantly, increased risks were also observed among patients with

hematological malignancies without records of such comorbidity. A more pronounced 6.5-fold increased risk of completed suicide was also noted among immigrants with hematological malignancies compared with cancer-free native residents (p for interaction 0.03).

Table 4. Relative risk* of attempted or completed suicide by potential effect modifying factors among patients with hematological malignancies compared with cancer-free individuals

	Attempted suicide			Completed suicide		
	No. of events	Incidence /10,000 py	IRR (95% CI)	No. of events	Incidence /10,000 py	IRR (95% CI)
History of mental disorder						
No - cancer free	268	3.19	1.00	105	1.25	1.00
Yes - cancer free	92	34.7	10.9 (8.57-13.9)	20	7.40	6.35 (3.94-10.2)
No - cancer	103	5.00	1.47 (1.16-1.85)	50	2.42	1.90 (1.35-2.68)
Yes - cancer	43	66.6	19.5 (14.0-27.2)	13	19.5	16.4 (9.12-29.5)
History of attempted suicide						
No - cancer free	304	3.54	1.00	117	1.40	1.00
Yes – cancer free	56	78.8	19.8 (14.7-26.6)	8	10.7	9.09 (4.42-18.7)
No - cancer	128	6.07	1.61 (1.30-1.99)	58	2.74	1.97 (1.43-2.73)
Yes - cancer	18	110	28.1 (17.2-45.9)	5	28.5	23.7 (9.68-57.9)

¹ Incidence Rate ratios (IRR) with 95% confidence intervals (CI), adjusted for sex, age, calendar period, education and migration status.

5.2 STUDY II

For details, please see the appended publication (PMID: 26537111). Among all patients, 40% were classified as having at least one comorbid disease. Patients with AML had the highest proportion (43%) and also the highest median age at diagnosis (72 years). Among patients above 80 years of age at diagnosis, the majority had a history of comorbid disease (AML 59%, CML 59%, myeloma 52%). Any comorbidity was associated with increased risks of all-cause as well as cancer-specific death among patients with AML and myeloma, and with a borderline increased risk among patients with CML. Renal disease was associated with an increased risk of cancer-specific death in all patient groups (Figure 1).

Acute myeloid leukemia (AML)

More specifically, in AML patients, a history of cerebrovascular, rheumatologic, renal, liver or psychiatric disease or dementia, was observed to be associated with a significantly higher AML-specific mortality compared with patients without the specified comorbid diseases in question. Using estimates from flexible parametric survival models to assess the stacked cumulative probability of cancer-specific and other-cause death accounting for competing risks during the first 5 years of follow-up, cancer-specific death dominated in men and women 60-89 years, irrespective of comorbidity. The cumulative probability of cancer-specific death in patients with comorbid disease was higher than in patients without comorbid disease in age

groups 60-69 and 70-79 years, but there was no difference by comorbidity in patients 80+ years of age.

Chronic myeloid leukemia (CML)

CML patients with a history of renal disorders had a significantly increased CML-specific mortality. Other diseases including cardiovascular, rheumatologic and liver disease were associated with nominally increased risks but were non-significant, perhaps due to small numbers. Having a history of comorbid disease was associated with higher 5-year cumulative probability of cancer-specific death among men 60-69 years and women 80-89 years. In other ages, no significant differences between patients with and without comorbid disease were observed. Among male CML patients >70 years of age, other-cause deaths were more common than CML-specific deaths.

Myeloma

Patients with myeloma and prior renal disease, cardiovascular diseases, cerebrovascular diseases, CPD, psychiatric diseases and dementia were at increased risk of myeloma-specific mortality compared to patients without these disorders, respectively. The probability of myeloma-specific death within 5 years after diagnosis of myeloma was higher in patients with comorbid disease than in those without comorbid disease in both sexes and all age groups studied (60-89 years).

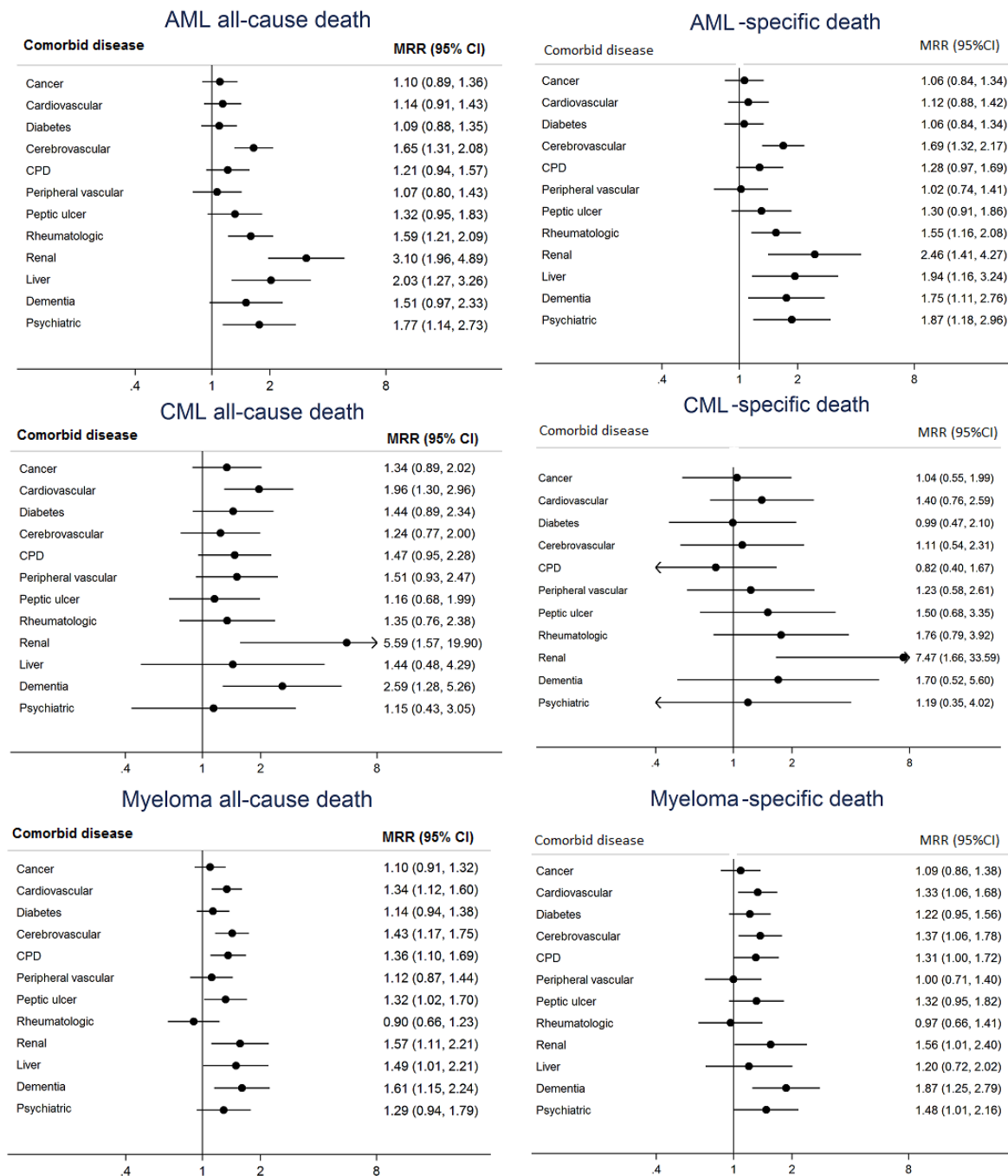


Figure 1. MRR for all-cause and cancer-specific death by type of comorbid disease

MRR: Mortality rate ratios adjusted for age (in 10 year intervals), country of birth, time since diagnosis, calendar year of diagnosis and number of comorbid diseases, sex and education level except when main effects of these factors were estimated **AML:** acute myeloid leukemia **CML:** chronic myeloid leukemia **CPD:** Chronic pulmonary disease

*Because of few patients with hemiplegia/paraplegia (n=49) and HIV/AIDS (n=2) overall, and with liver disease in CML, results for these groups are not presented.

5.3 STUDY III:

For details, please see the appended unpublished manuscript. Among the 3,177 patients with DLBCL, 40% of the patients had a history of at least one of the comorbid diseases assessed, and 13% had a history of two or more diseases. Any comorbidity was associated with higher relative probability of presenting with low performance status, and high international prognostic index (IPI) score compared with patients without comorbidity at diagnosis of DLBCL. There were no apparent differences in the relative distribution by stage at diagnosis, elevated LD or unfavorable extranodal locations by comorbidity. Further, there was a large difference in treatment intent. Among patients without comorbidity, 86% of the patients were selected for primary treatment with curative intent, whereas only 68% of the patients with comorbid disease received primary curative treatment (RRR=0.48, 95% CI=0.38-0.60).

Table 5. Relative risk (odds ratio, OR) of being diagnosed with stage III-IV diffuse large B-cell lymphoma (DLBCL) versus stage I-II, and being selected for treatment with curative versus palliative intent among patients with specific types of comorbid diseases compared with no comorbid disease.

	All patients	
	Stage III-IV versus I-II	Curative versus palliative treatment intent
	OR (95% CI)	OR (95% CI)
Type of comorbid disease		
No comorbid disease	1.00 (reference)	1.00 (reference)
Solid cancer	0.87 (0.69-1.10)	0.56 (0.40-0.77)
Cardiovascular disease	0.83 (0.60-1.15)	0.50 (0.33-0.76)
Diabetes	0.83 (0.61-1.12)	0.77 (0.50-1.20)
Cerebrovascular disease	0.79 (0.54-1.11)	0.66 (0.41-1.05)
Chronic pulmonary disease	1.24 (0.85-1.82)	0.40 (0.24-0.66)
Peptic ulcer disease	1.00 (0.65-1.53)	0.89 (0.48-1.65)
Rheumatologic disease	1.11 (0.71-1.75)	0.59 (0.31-1.11)
Peripheral vascular disease	1.00 (0.57-1.77)	0.61 (0.30-1.24)
Psychiatric disorders	1.66 (0.89-3.08)	0.27 (0.12-0.59)
Liver disease	1.61 (0.79-3.27)	0.24 (0.10-0.57)
Renal disease	1.18 (0.59-2.38)	0.41 (0.17-0.97)
Dementia	0.41 (0.16-1.07)	0.19 (0.07-0.48)
Hemiplegia/Paraplegia	0.71 (0.28-1.82)	0.34 (0.10-1.20)

Dementia, psychiatric disorders, liver disease, chronic pulmonary disease, cardiovascular disease and solid cancer were strongly associated with lower probability of receiving curative treatment compared with those without comorbid disease.

Among all patients, comorbidity was associated with risk of all-cause, lymphoma-specific as well as other-cause death (Table 6), likely mediated by differences in treatment intent. Among

patients selected for treatment with curative intent, comorbidity was associated with all-cause and other-cause deaths, but not with lymphoma-specific deaths (Table 6).

Table 6. Mortality rate ratios (MRR)* for all-cause, lymphoma-specific and other-cause death by number of comorbid diseases, host and disease characteristics among diffuse large B-cell lymphoma (DLBCL) patients diagnosed between 2004 to 2009. MRRs are presented among all patients, and separately among patients treated with curative intent.

	ALL PATIENTS			PATIENTS TREATED WITH CURATIVE INTENT		
	All-cause death	Lymphoma-specific death	Other-cause death	All-cause death	Lymphoma-specific death	Other-cause death
	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)
No. of comorbid diseases						
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.34 (1.17-1.53)	1.25 (1.06-1.46)	1.61 (1.25-2.08)	1.20 (1.03-1.41)	1.11 (0.92-1.34)	1.43 (1.07-1.91)
2+	1.73 (1.48-2.03)	1.43 (1.18-1.73)	2.81 (2.12-3.73)	1.62 (1.34-1.97)	1.21 (0.95-1.55)	2.91 (2.12-4.01)
Sex						
Men	1.00	1.00	1.00	1.00	1.00	1.00
Women	0.87 (0.78-0.98)	0.84 (0.74-0.96)	0.96 (0.77-1.20)	0.88 (0.77-1.01)	0.85 (0.72-0.99)	0.97 (0.76-1.24)
Education level						
0-9	1.00	1.00	1.00	1.00	1.00	1.00
10-12	0.90 (0.79-1.03)	0.85 (0.73-0.99)	1.05 (0.82-1.35)	0.92 (0.79-1.07)	0.89 (0.74-1.07)	0.98 (0.74-1.29)
>12	0.96 (0.81-1.13)	0.91 (0.75-1.10)	1.08 (0.79-1.45)	1.02 (0.85-1.23)	1.01 (0.81-1.25)	1.02 (0.72-1.44)
Performance status						
Asymptomatic	1.00	1.00	1.00	1.00	1.00	1.00
Symptoms – ambulatory	1.62 (1.39-1.89)	1.79 (1.48-2.17)	1.34 (1.02-1.76)	1.70 (1.44-2.02)	1.94 (1.57-2.40)	1.34 (0.99-1.79)
<50% in bed	2.20 (1.80-2.69)	2.44 (1.92-3.11)	1.85 (1.26-2.70)	2.05 (1.62-2.60)	2.24 (1.68-2.99)	1.86 (1.20-2.88)
>50% in bed/bedbound	4.54 (3.78-5.44)	5.35 (4.31-6.63)	2.85 (1.95-4.17)	3.39 (2.71-4.23)	4.00 (3.08-5.20)	2.20 (1.40-3.47)
S-lactate dehydrogenase (LD)						
Normal	1.00	1.00	1.00	1.00	1.00	1.00
Elevated	1.41 (1.23-1.61)	1.50 (1.28-1.77)	1.21 (0.95-1.55)	1.40 (1.19-1.64)	1.52 (1.25-1.85)	1.17 (0.89-1.54)
Bulky disease						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.15 (1.00-1.31)	1.21 (1.03-1.41)	0.97 (0.73-1.30)	1.19 (1.02-1.40)	1.26 (1.05-1.51)	1.03 (0.74-1.42)
Stage**						
Stage I	1.00	1.00	1.00	1.00	1.00	1.00
Stage II	0.90 (0.74-1.09)	0.98 (0.76-1.26)	0.82 (0.60-1.13)	0.82 (0.66-1.02)	0.84 (0.63-1.13)	0.82 (0.58-1.17)
Stage III	1.05 (0.85-1.29)	1.28 (0.99-1.66)	0.78 (0.54-1.13)	1.01 (0.80-1.27)	1.16 (0.86-1.55)	0.86 (0.57-1.29)
Stage IV	0.92 (0.76-1.12)	1.20 (0.94-1.53)	0.53 (0.37-0.75)	0.84 (0.68-1.05)	1.07 (0.81-1.41)	0.51 (0.34-0.77)
Major extranodal disease†						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.74 (1.50-2.03)	1.73 (1.45-2.07)	1.79 (1.31-2.44)	1.66 (1.39-1.99)	1.67 (1.36-2.06)	1.65 (1.15-2.35)

*MRR=Mortality rate ratios adjusted for age, country of birth, time since diagnosis, calendar year of diagnosis, sex, education level, performance status, stage, LD, bulky disease, extranodal disease and comorbidity

**Stage I: AA1, PeI; Stage II: AA2, PeII, PeII1, PeII2; Stage III: AA3; Stage IV: AA4

† Extranodal locations known to be associated with poor prognosis (including central nervous system (CNS), bone marrow, lung and gastrointestinal sites including liver)

5.4 STUDY IV

For details, please see the appended publication (PMID: 26652908). Among the 337,437 individuals appendectomized before the age of 60 years, the majority (82%) were also younger than 40 years at surgery, and 42% were younger than 20 years. We found no increased risk of NHL, HL, CLL, myeloma or ALL associated with appendectomy *per se* relative to the general population in Sweden. In a stratified analysis, patients diagnosed with appendicitis after appendectomy were at a statistically significant increased risk of HL (SIR=1.29, 95% CI=1.07-1.54), based on 122 observed HL cases. In patients appendectomized from 1993 and onwards where risks of lymphoma subtypes could be classified in more detail, an increase risk was noted for the nodular sclerosis subtype of HL in association with appendicitis (SIR=1.55, 95% CI=1.01-2.27). An increase was also noted for HL among individuals appendectomized below the age of 20 years. A statistically significant risk increase was also noted for myeloma among men.

Table7. Relative risk* of lymphoid neoplasms** among appendectomized patients <60 years of age stratified by sex, age, duration of follow-up, calendar period of appendectomy and medical diagnoses 1975-2009 in Sweden

	NHL		HL		CLL		Myeloma		ALL	
	N	SIR (95%CI)	N	SIR (95%CI)	N	SIR (95%CI)	N	SIR (95%CI)	N	SIR (95%CI)
Overall	448	0.97 (0.88-1.06)	144	1.14 (0.96-1.34)	93	0.87 (0.70-1.06)	156	1.14 (0.96-1.33)	45	1.10 (0.80-1.47)
Sex										
Men	251	0.90 (0.79-1.02)	80	1.15 (0.91-1.43)	62	0.89 (0.68-1.14)	102	1.24 (1.01-1.50)	23	0.97 (0.61-1.45)
Women	197	1.07 (0.92-1.23)	64	1.13 (0.87-1.44)	31	0.83 (0.56-1.18)	54	0.99 (0.74-1.29)	22	1.28 (0.80-1.93)
Age at appendectomy										
0-19 years	56	0.94 (0.71-1.22)	76	1.18 (0.93-1.48)	2	0.76 (0.09-2.76)	5	1.00 (0.32-2.33)	23	1.08 (0.68-1.61)
20-39 years	166	1.00 (0.85-1.16)	50	1.11 (0.82-1.46)	23	0.74 (0.47-1.11)	44	1.06 (0.77-1.42)	13	1.07 (0.57-1.83)
40-59 years	226	0.95 (0.83-1.09)	18	1.08 (0.64-1.70)	68	0.93 (0.72-1.17)	107	1.18 (0.97-1.42)	9	1.20 (0.55-2.28)
Duration of follow-up										
1-4 years	71	1.04 (0.81-1.31)	44	1.25 (0.91-1.68)	18	1.58 (0.94-2.50)	25	1.57 (1.02-2.32)	13	0.91 (0.49-1.56)
5-9 years	81	1.01 (0.80-1.25)	35	1.06 (0.74-1.48)	10	0.64 (0.31-1.17)	16	0.75 (0.43-1.22)	8	0.87 (0.38-1.71)
10-14 years	84	0.97 (0.77-1.20)	31	1.22 (0.83-1.74)	16	0.85 (0.49-1.38)	30	1.20 (0.81-1.71)	9	1.39 (0.64-2.64)
15-26 years	170	0.97 (0.83-1.13)	27	0.96 (0.63-1.40)	39	0.84 (0.60-1.15)	64	1.13 (0.87-1.44)	12	1.31 (0.68-2.29)
26+ years	42	0.81 (0.58-1.10)	7	1.50 (0.60-3.09)	10	0.67 (0.32-1.23)	21	1.15 (0.71-1.76)	3	1.50 (0.31-4.37)
Calendar period of appendectomy										
1975-1989	322	0.94 (0.84-1.05)	92	1.10 (0.89-1.35)	70	0.86 (0.67-1.09)	111	1.05 (0.87-1.27)	28	1.08 (0.71-1.55)
1990-1999	102	1.04 (0.85-1.27)	41	1.21 (0.87-1.64)	19	0.90 (0.54-1.40)	39	1.50 (1.07-2.05)	15	1.31 (0.73-2.16)
2000-2009	24	1.02 (0.65-1.52)	11	1.25 (0.62-2.24)	4	0.88 (0.24-2.25)	6	1.02 (0.37-2.21)	2	0.57 (0.07-2.05)
Medical diagnosis										
Appendicitis only	327	0.92 (0.83-1.03)	122	1.29 (1.07-1.54)	69	0.83 (0.65-1.05)	116	1.10 (0.91-1.32)	34	1.10 (0.76-1.54)
Appendicitis with other medical diagnoses	36	1.35 (0.95-1.87)	4	0.69 (0.19-1.78)	8	1.21 (0.52-2.39)	11	1.30 (0.65-2.33)	4	2.05 (0.56-5.24)
Mesenteric lymphadenitis	19	1.27 (0.77-1.99)	9	0.92 (0.42-1.74)	3	1.70 (0.35-4.96)	4	1.51 (0.41-3.88)	3	0.95 (0.20-2.78)
Other diagnoses	66	0.98 (0.76-1.24)	9	0.57 (0.26-1.08)	13	0.83 (0.44-1.43)	25	1.21 (0.78-1.78)	4	0.78 (0.21-1.99)
Appendicitis spectrum										
Non-perforated	293	0.94 (0.83-1.05)	111	1.28 (1.05-1.54)	66	0.92 (0.71-1.17)	107	1.17 (0.96-1.41)	32	1.15 (0.79-1.62)
Perforated/ abscessed	70	1.03 (0.80-1.30)	15	1.09 (0.61-1.80)	11	0.61 (0.30-1.09)	20	0.89 (0.54-1.37)	6	1.22 (0.45-2.65)

* Relative risk was assessed as the standardized incidence ratio (SIR) with 95% confidence interval (CI)** Also includes 6 patients with unspecified lymphoma.

NHL=Non-Hodgkin lymphoma, HL=Hodgkin lymphoma, CLL=Chronic lymphocytic leukemia, ALL=Acute lymphoblastic leukemia. Patients with diagnosis of a lymphoid neoplasm during the first year after appendectomy were excluded.

6 DISCUSSION

6.1 INTERPRETATION OF FINDINGS

6.1.1 Study I

In this study, risks of attempted and completed suicide were significantly increased in patients diagnosed with hematological malignancies compared with cancer free individuals, and the risks were most pronounced for patients with myeloma. Risk levels among hematological malignancy compared to cancer free individuals were similar to those among solid cancer patients compared to cancer-free individuals. Risks in patients with myeloma appeared to be higher than among other solid cancer patients on average, although no direct formal comparison was made contrasting these patient groups

The association between a diagnosis of a hematological malignancy and risk of completed suicide has been investigated in several previous studies [17-25]. A few have attempted to estimate risk in patient subgroups of hematological malignancies including myeloma, AML, HL and NHL [21, 22]. In line with our findings, Kendal et al. noted a higher rate of completed suicide for myeloma than leukemia and lymphoma [24]. Mental disorders, severe illness and advanced stage of disease are known risk factors for suicide in the general population and also in cancer patients [23, 100, 145-149]. The higher risk of suicide in myeloma could be associated with the often severe symptoms of myeloma such as bone pain and functional disability and the incurable prognosis [150-153], since pain, physical symptoms and prognosis are plausible triggers for suicide ideation [17]. Health care personnel working with hematological malignancy patients (as well as those working with other cancer patients) should be aware of the increased risk of attempted and completed suicide in patients with increased susceptibility (previous mental disorders and suicide attempts, immigrants) as well as those with bad prognosis and disabling symptoms (among hematological malignancies myeloma in particular).

6.1.2 Study II

Comorbidity is an established predictor of prognosis in solid cancers [109-113] and hematological malignancies [8-13] especially among patients eligible for hematopoietic stem cell transplantation [14-16]. Previous studies of the association of comorbidity with hematological malignancy outcomes have often focused on overall survival rather than progression-free or cancer-specific survival, and have also often been too small in size to investigate associations with separate comorbid disorders.

6.1.2.1 AML

A favorable outcome of treatment in AML, i.e. complete remission and long-term survival can be achieved in a subgroup of patients through intensive chemotherapy, the tolerability and administration of which depends on age and performance status [154, 155]. In previous

studies on elderly (65+ years) AML patients, a worse overall survival has been reported for patients with comorbid diseases using the Charlson comorbidity index (CCI)[10-12, 65, 156, 157]. Etienne et al. also showed that comorbid diseases (CCI>1) are predictors of complete remission [12] and others reported a decrease in the chances of receiving intensive chemotherapy with increasing number of comorbid disease [13, 157]. Potential differences in outcome by type of comorbidity was not explored in these studies beyond the weighting of disorders built into the CCI. The specific comorbidities associated with AML-specific mortality in this study are plausibly linked with a lower tolerance for intensive remission-induction regimens at an organ-level (renal and liver disease) or with a presumed lower tolerability and compliance to intensive chemotherapy in general (cerebrovascular and psychiatric disease, dementia) [13]. On the other hand, common comorbidities such as diabetes, cardiovascular disease and previous cancer were not significantly associated with a worse treatment outcome, although large individual variations are of course likely depending on the severity of the disease. Contrary to a wide-spread belief that comorbidity represents a clinical challenge mostly in the oldest patients, we further showed that any comorbidity was associated with a higher probability of AML-specific death mainly among patients aged 60 to 69 years, but not among patients 80-89 years. This finding likely reflects differences in treatment intentions and tumor biology by age [158].

6.1.2.2 CML

Although tyrosine kinase inhibitors have improved survival in CML in the 21st century, 5-year survival is still around 60% [69, 159]. Previous studies of the impact of comorbid disease on CML prognosis in the tyrosine kinase era, suggest a major effect of aging and increased frequency of other-cause deaths rather than CML-specific deaths [160]. Another concern is that patients with comorbid disease may not be eligible to start tyrosine kinase inhibitors. We observed that prior renal disease in particular was associated with increased CML-specific death, which may be mediated through dose reductions or caution to prescribe tyrosine kinase inhibitors [67, 161]. Our findings of a negative impact of comorbid disease on overall survival was in line with previous studies [156, 160, 162, 163] but additionally showed that other-cause deaths outnumbered CML-specific deaths regardless of comorbidity in male patients above the age of 70 years, which may have implications for treatment decisions at an individual level. On the other hand, women were more likely to die of CML rather than other causes up to 89 years of age, potentially indicating under treatment in these patients [159].

6.1.2.3 Myeloma

Survival in myeloma patients has improved in later years due to several factors including more intensive treatment schemes and hematopoietic-cell transplantation as well as better supportive care [164, 165]. Comorbidity has been reported to be associated with overall survival in previous studies [166, 167]. According to these previous reports, renal disorder and lung disease are particularly important determinants for myeloma outcome [166-168]. Our results from study of ~4500 myeloma patients confirm the prognostic implications of

history of renal and pulmonary disease, in addition to pointing to associations with cardiovascular and cerebrovascular disease, dementia and psychiatric disorders.

6.1.3 Study III

In our study, patients with a history of comorbid diseases presented with worse performance status and higher IPI score and lower chance of receiving curative treatment at DLBCL diagnosis, than other patients.

DLBCL patients with comorbid disease have been shown in some previous studies to have decreased overall survival [112, 169-173]. One study also showed a higher likelihood of receiving palliative treatment in patients with higher adult comorbidity-27 score disease [170]. Another study on DLBCL patients noted a higher risk of toxicity in patients with high Charlson comorbidity index [169]. In our study, comorbid disease was further associated with increased risk of lymphoma-specific death, in line with the lower treatment response rate also reported in two previous smaller investigations [112, 171]. However, most previous studies have been small (median N=165, range 41-387) as reviewed by Terret et al. in 2015 [174], and have not evaluated treatment selection or outcome in relation to specific comorbid diseases.

Cardiovascular and chronic pulmonary disorders and dementia were associated both with selection of palliative rather than curative treatment, as well as with lymphoma-specific death. In a questionnaire based study, cognitive disorders and functional status affected hematologists' treatment selection [175] supporting our findings. Association between cardiovascular disorders and lymphoma-specific death points to need the less cardiotoxic treatments. Optimizing the patients with cardiovascular disorders before treatment with cardiotoxic agents like doxorubicin may also be helpful [176].

6.1.4 Study IV

Overall, we did not observe any strong associations between appendectomy and excess risk of lymphoid neoplasms, although we did find an increased risk of HL in patients diagnosed with appendicitis rather than appendectomy per se. We also observed an increased risk of myeloma among men, which was however confined to the first few years of follow up and may be explained by surveillance bias.

In the 1960s, two studies reported an association between appendectomy and risk of HL [3, 4]. Later, in 2009, Cozen et al. also reported a positive association in a case-control study among twins HL [7]. In the 1960s-1980s three other studies reported no association between appendectomy and risk of HL [130-132]. In 1998, Møller et al. in a large register-based cohort did not observe relation between appendectomy and risk of leukemia, myeloma, HL and NHL [5]. However, Cope et al. [6] reported a border-line significantly increased risk of NHL in appendectomized children and more evidently in patients diagnosed as appendicitis [6].

Given the result of previous studies [5, 131, 177], and our findings, there is on the whole no evidence of associations between appendectomy and risk of lymphoid neoplasms except the possible relation between appendicitis and HL. Appendix is a closed-end lumen rich in lymphoid tissue [178, 179] and microbial agents, and is therefore at risk of local infection and inflammation. Patients with chronic inflammation in the setting of autoimmune diseases are at a higher risk of HL [180-182]. Also, the Epstein-Barr virus (EBV), an established factor in the etiology of HL [183], has been found in appendix [184]. An increased risk of appendicitis has also been reported in teenagers following infectious mononucleosis [185]. Genetic variation in the HLA-DRB1 region has been linked with several inflammatory conditions and infections [186-188] as well as with risk of EBV-negative classical HL [189, 190]. Hence the higher risk of HL in appendicitis might be explained by possible biologic mechanisms or through shared genetic susceptibility.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Study I

In this study, we assembled a large cohort of patients with hematological malignancies, and carefully matched to population comparators with the same birth year, and sex and who were alive and cancer-free at the time of the cancer diagnosis of the case. The large size of the study overall ensured sufficient number of events to adjust for several possible confounders for which data was also available (education level, mental disorders, migration status). However, although the number of events was fairly large overall, estimates of relative risk became imprecise in some subgroup analyses, notably for patients with leukemias, and also hampered detailed studies of interaction. Also, we may have a problem of misclassification of the outcome, especially of attempted suicide, in that hospital admissions for illness associated with suicide attempts may have been interpreted and coded as something else. Also, sometimes, people may not seek health care for attempted suicide.

6.2.2 Study II

The main limitation of this study was lack of information about more refined molecular subtypes of AML carrying prognostic information, clinical patient-related factors such as performance status and treatment-related factors. It is not entirely clear however, to what extent such factors could represent confounding factors or rather effect modifying factors in the association between comorbidities and hematological malignancy outcome. For example, performance status at leukemia/myeloma diagnosis is likely influenced both by comorbid diseases and the malignancy itself.

To minimize the misclassification bias due to possible error in reporting cause of death in different calendar periods we adjusted the analysis for calendar period. Although the quality of the cause of death register has been found to be generally high among cancer patients, some leukemia/myeloma deaths may have been erroneously classified as other cause death and vice versa, making exact proportions uncertain. Also, researchers may use different definitions of cancer-specific as opposed to other-cause deaths. Our aim was to define deaths

as cancer-specific when death was a result of progressive malignancy, and all other deaths as due to other causes. However, other-cause deaths then include a mix of deaths due to treatment toxicity (indirectly cancer-related) and unrelated deaths.

The assessment of comorbidity histories through the Patient register has also resulted in some misclassification and misrepresentation of the whole spectrum of comorbid disorders, since many milder comorbid diseases are managed primarily in primary health care not captured by this register. Hence, the results are likely to represent associations with comorbidities towards the severe end of the spectrum.

6.2.3 Study III

In this study, we had access to detailed clinical data through the national quality register for lymphoma, with improved possibility to control for confounding as well as to investigate mediating factors of worse outcomes. The small number of patients for some groups of comorbidities is a source of low power and implies a risk of missing true associations.

Apart from some possible misclassification comorbid disease and causes of death as discussed above, the clinical data may also have been misclassified to some extent. However, in an unpublished validation study (personal communication Dr Szekely), high concordances were found for most factors relating to lymphoma characteristics at presentation.

6.2.4 Study IV

The major concern with this study is the large number of analyses performed and estimates presented. Given the multiple comparisons, some significant results may have arisen due to chance alone. However, the increased risk, observed for HL, was strengthened by biological plausibility. Also, the lack of information on subtypes of NHL and HL through snomed codes limited the analyses of subtype-specific risks to 1993-2009, which reduced the power for these analysis.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 CONCLUSIONS

- Risk of attempted and completed suicide is increased in patients diagnosed with myeloma and lymphoma.
- Subgroups of patients with hematological malignancies (as well as other cancer patients) should be monitored for suicidal ideation based on individual susceptibility (e.g., mental comorbidity) and symptoms/prognosis (e.g. myeloma).
- Patients with comorbidity prior to AML, CML and myeloma had higher all-cause as well as cancer-specific mortality compared with patients without comorbidity.
- Comorbidities associated with organ failure (most importantly renal disease) or cognitive function (cerebrovascular and psychiatric diseases and dementia) were associated with worse outcomes in several hematological malignancy subtypes.
- In patients diagnosed with DLBCL, a history of comorbid disease was associated with a lower likelihood of receiving curative treatment.
- In patients with DLBCL treated with curative intent, comorbid disease history was associated with all-cause but not lymphoma-specific death.
- Appendicitis but not appendectomy per se may be associated with a small increased risk of HL, but otherwise there's little evidence that appendectomy is associated with risk of lymphoid malignancies.

7.2 FUTURE PERSPECTIVES

- Patients diagnosed with hematological malignancies and other cancer forms are at risk of suicide. Intervention studies are needed in order to evaluate how we best can monitor, prepare and support the patients to reduce risk of suicidal events.
- Future prognostic indices in patients with hematological malignancies should consider the inclusion of hematological malignancy-subtype-specific comorbid disease groups to improve prognostic prediction and treatment channeling.
- Studies are needed to further investigate how clinicians can optimize patients with specific comorbid diseases to improve tolerance of intensive chemotherapy.
- The treatment for hematological malignancies needs to be improved with use of more effective and at the same time less toxic agents. In this regard, the current development of a wide range of new therapeutic agents including targeted biological therapy for cancer including several hematological malignancies, holds promise for the future.
- Risk factors for lymphoid malignancies are incompletely known, but do not appear to include surgical resection of lymphoid organs such as the appendix.

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